NICKEL AND ITS COMPOUNDS – POTENTIAL FOR OCCUPATIONAL HEALTH ISSUES

Position Paper

PREPARED BY
AIOH Exposure Standards Committee
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AUTHORISATION
This Position Paper has been prepared by the AIOH Exposure Standards Committee and authorised by AIOH Council.

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AUSTRALIAN INSTITUTE OF OCCUPATIONAL HYGIENISTS INC (AIOH)

The Australian Institute of Occupational Hygienists Inc. (AIOH) is the association that represents professional occupational hygienists in Australia. Occupational hygiene is the science and art of anticipation, recognition, evaluation and control of hazards in the workplace and the environment. Occupational hygienists specialise in the assessment and control of:

- Chemical hazards (including dusts such as silica, carcinogens such as arsenic, fibrous dusts such as asbestos, gases such as chlorine, irritants such as ammonia and organic vapours such as petroleum hydrocarbons);
- Physical hazards (heat and cold, noise, vibration, ionising radiation, lasers, microwave radiation, radiofrequency radiation, ultra-violet light, visible light); and
- Biological hazards (bacteria, endotoxins, fungi, viruses, zoonoses).

Therefore, the AIOH has a keen interest in the potential for workplace exposures to nickel and its compounds, as its members are the professionals most likely to be asked to identify associated hazards and assess any exposure risks.

The Institute was formed in 1979 and incorporated in 1988. An elected governing Council, comprising the President, President Elect, Secretary, Treasurer and three Councillors, manages the affairs of the Institute. The AIOH is a member of the International Occupational Hygiene Association (IOHA).

The overall objective of the Institute is to help ensure that workplace health hazards are eliminated or controlled. It seeks to achieve this by:

- Promoting the profession of occupational hygiene in industry, government and the general community.
- Improving the practice of occupational hygiene and the knowledge, competence and standing of its practitioners.
- Providing a forum for the exchange of occupational hygiene information and ideas.
- Promoting the application of occupational hygiene principles to improve and maintain a safe and healthy working environment for all.
- Representing the profession nationally and internationally.

More information is available at our website – http://www.aioh.org.au.

EXPOSURE STANDARDS COMMITTEE MISSION STATEMENT

The AIOH established the Exposure Standards Committee to provide expert guidance and comment to the exposure standards setting process at a State and National level, and internationally where appropriate, through development of AIOH Position Papers, AIOH guidance publications or comment on relevant Standards, Regulations and Codes of Practice. The Committee's remit is to confirm that the exposure standards numbers, and Standards and Codes of Practice, are changed for valid occupational hygiene and scientific reasons.

STATEMENT OF POSITION REGARDING AIOH POSITION PAPERS

The AIOH is not a standards setting body. Through its Position Papers, the AIOH seeks to provide relevant information on substances of interest where there is uncertainty about existing Australian exposure standards. This is done primarily through a review of the existing published, peer-reviewed scientific literature but may include anecdotal evidence based on the practical experience of certified AIOH members. The Position Papers attempt to recommend a health-based exposure value that can be measured; that is, it is technically feasible to assess workplace exposures against the derived OEL. It does not consider economic or engineering feasibility. As far as reasonably possible, the AIOH formulates a recommendation on the level of exposure that the typical worker can experience without adverse health effects.

Any recommended exposure value should **not** be viewed as a fine line between safe and unsafe exposures. They also do not represent quantitative estimates of risk at different exposure levels or by different routes of exposure. Any recommended exposure value should be used as a guideline by professionals trained in the practice of occupational hygiene to assist in the control of health hazards.

CONSULTATION WITH AIOH MEMBERS

AIOH activities are managed through committees drawn from hygienists nationally. This Position Paper has been prepared by the Exposure Standards Committee, with comments sought from AIOH members generally and active consultation with particular members selected for their known interest and/or expertise in this area. Various AIOH members were contributors in the development of this Position Paper. Key contributors included: Tim White, Kevin Hedges and Ian Firth.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACGIH	American Conference of Governmental Industrial Hygienists
AIOH	Australian Institute of Occupational Hygienists
AM	Arithmetic mean
AS	Australian Standard
AS/NZS	Australian and New Zealand Standard
BEI	Biological Exposure Index
BGV	Biological Guidance Value
DFG	Deutsche Forschungsgemeinschaft
EC	European Commission
EFSA	European Food Safety Authority
GM	Geometric mean
GSD	Geometric standard deviation
HPAL	High pressure acid leaching
HSE	Health and Safety Executive (United Kingdom)
HSIS	Hazardous Substances Information System
IARC	International Agency for Research on Cancer
ICNCM	International Committee on Nickel Carcinogenesis in Man
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
ICP-MS	Inductively coupled plasma mass spectrometry
ILO	International Labour Organization
kt	kilotonnes
LEV	Local Exhaust Ventilation
LOAEL	Lowest Observed Adverse Effect Level
LoQ	Limit of Quantitation
mg/m^3	milligrams (10^{-3} g) per cubic metre
μ	micro-, (10^{-6}) as in micrometre (μm)
μg	microgram (10^{-6} g)
NIC	Notice of Intended Changes
NIOSH	National Institute for Occupational Safety and Health
NiPERA	Nickel Producers Environmental Research Agency
NOAEL	No Observed Adverse Effect Level
NTP	National Toxicology Program of the US Department of Health and Human Services, Public Health Service
OEL	Occupational Exposure Limit
PPE	Personal Protective Equipment
REL	Recommended Exposure Limit
SCOEL	Scientific Committee on Occupational Exposure Limits (EC)
SMR	Standardised mortality ratio
SWA	Safe Work Australia
TDI	Tolerable daily intake
TLV	Threshold Limit Value
TWA	Time Weighted Average
URL	Upper reference level
UK	United Kingdom
US	United States
WES	Workplace Exposure Standard
XRF	X-ray fluorescence

AIOH POSITION ON NICKEL AND ITS COMPOUNDS AND THEIR POTENTIAL FOR OCCUPATIONAL HEALTH ISSUES

Key messages

- Nickel at high concentrations is a respiratory health hazard likely to cause cancer and is also known to cause dermatitis and sensitivity in some people.
- The AIOH believes that exposure may be adequately controlled by conventional means such as local exhaust ventilation and segregation of workers from areas of high concentration.
- A standard to limit exposure to no more than 0.1 mg of Ni in each cubic metre of air is recommended for all forms of nickel.

Summary

This paper was compiled to give guidance on the assessment, evaluation and control of occupational exposure to nickel and its commonly encountered compounds, with an emphasis on recommending a health-based occupational exposure limit (OEL). The current Safe Work Australia (SWA) workplace exposure standards (WES) and current international OELs are discussed and the possible health effects examined.

Nickel is a naturally occurring, lustrous, silvery-white metallic element. It is the fifth most common element on earth. Major uses have included production of stainless steel, corrosion and heat resistant alloys, catalysts for hydrogenation of fats and oils, electroplating, coinage and alkaline (NiCad) batteries. Inhalation is the main route of exposure to nickel in industry, although ingestion of nickel dust from contaminated skin may also be an exposure route.

The current SWA WES for nickel and its compounds is a time weighted average (TWA) value as set out below, based on the 1991 American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV®):

Nickel, metal & powder	1.0 mg/m³	Carcinogen Category 3, Sensitiser
Nickel, soluble compounds (as Ni)	0.1 mg/m³	Carcinogen Category 1, Sensitiser
Nickel sulphide roasting (fume & dust) (as Ni)	1.0 mg/m³	Carcinogen Category 1, Sensitiser

Nickel compounds have long been recognised as causing cancers of the lung, nasal cavity and paranasal sinuses, and of being a sensitiser. In 2012, the International Agency for Research on Cancer (IARC) classified nickel compounds as being carcinogenic to humans (Group 1) and metallic nickel as possibly carcinogenic to humans (Group 2B).

For nickel compounds in general, the main adverse health effects are respiratory cancer (of the lung and nasal cavity and para-nasal sinus) and sensitisation leading to contact dermatitis. However, it should be noted that there is disparity in the literature and between organisations on what are the main health endpoints. Different organisations have used different critical effects to derive exposure limits.

There is no consensus view of nickel species' OELs. World authorities have set OELs using a range of methodologies. The current ACGIH TLVs are 1.5 mg/m³ for inhalable nickel as elemental or metal forms; 0.1 mg/m³ for inhalable soluble nickel compounds and nickel sub-sulphide (intermediate solubility); and 0.2 mg/m³ for inhalable insoluble nickel compounds.

The compounds principally implicated in causing respiratory cancer are sulphidic nickel, particularly nickel sub-sulphide (Ni_3S_2) and oxidic nickel, which includes a range of insoluble nickel compounds. There is debate about whether soluble nickel compounds are carcinogenic.

One of the most extensive studies on nickel exposures was carried out at Clydach Refinery in South Wales. This study followed 2521 men who had worked at the refinery for more than 5 years between 1902 and 1969. It showed clear evidence of nasal and lung cancer. These workers had been exposed to "relatively high" concentrations of airborne nickel. As the workers were tracked over time and exposures were greatly reduced, follow-up studies demonstrated negligible risks from "total nickel" at concentrations < 0.2 mg/m³. It was also found from this study that it was difficult to assign a risk to individual forms of nickel. It is now known that the risk is greater when there is exposure to mixed species of nickel.

Another study of workers in Kristiansand Norway demonstrated an excess risk of lung cancer with increasing exposure to soluble nickel and nickel oxide. This trend was seen for workers exposed to ≥ 1 mg/m³ x year of total nickel when compared with individuals from the general population. However, lung and nasal cancers were only significant for workers exposed to ≥ 15 mg/m³ x year "soluble nickel". Most of the risk was found where workers had concomitant exposures including exposure to nickel oxide ≥ 5 mg/m³ x year.

There are difficulties and uncertainties in using epidemiological data to estimate levels (and types) of nickel exposure that correspond to increased respiratory cancer risk in nickel refinery workers. Never the less, human studies are preferred for informing derivation of a plausible OEL. For the most part, different studies of workers occupationally exposed to nickel are reasonably consistent in suggesting that increased lung cancer risk occurs at inhalable nickel concentrations that are well above 0.1 mg/m³.

From animal studies, the most sensitive test species (the rat) has shown evidence of carcinogenicity at 0.1mg/m³ and above for nickel sub-sulphide, which is considered one of the most hazardous forms of nickel. Other hazards associated with nickel, as demonstrated in animal studies, include reproductive toxicity (including birth defects and spontaneous abortions) and skin sensitisation. However, human studies have not unequivocally demonstrated an association between nickel exposures and reproductive outcomes.

Recent information has also indicated that exposure to relatively low concentrations of nickel via the oral route (ingestion) can exacerbate adverse health effects in nickel-sensitised individuals.

The most effective means of restricting nickel uptake is by controlling exposure. The hierarchy of controls must be utilised when determining the appropriate controls to be utilised; for example:

- provision of improved enclosure and ventilation to capture fume and particulate,

- good housekeeping,

- provision and use of change room facilities for good personal hygiene,

- no eating or smoking in nickel-contaminated areas,

- administrative controls (e.g. limits on overtime),

- education and

- use of protective clothing and appropriate respiratory protection.

Engineering controls must always be accompanied by a preventative maintenance program to ensure that the equipment's performance is maintained at the design specification and checked on a regular basis.

The AIOH regards respiratory cancer (lung and nasal) as the main adverse health effect to derive an OEL recommendation. The TWA OEL for nickel (including both readily soluble and sparingly soluble (insoluble) compounds) recommended by the AIOH is 0.1 mg/m^3, to be measured as the inhalable aerosol fraction according to AS 3640. This standard is set to minimise the incidence of lung and nasal cancer.

Recent research undertaken by the UK HSE has demonstrated the value of using urinary nickel as a measure of control effectiveness for workplaces where skin contamination, hence inadvertent hand mouth contact and ingestion, may be an issue (i.e. electroplating).

1. What is nickel?

Nickel is a naturally occurring, lustrous, silvery-white metallic element. It is the fifth most common element on earth and occurs extensively in the earth's crust, although most nickel is inaccessible in the core of the earth. Nickel does not occur in nature by itself but it is associated with cobalt or as an alloy with copper, zinc, iron or arsenic. It occurs in nature principally as oxides (laterites), sulphides and silicates.

Industrially important properties of nickel include: high melting point, resists corrosion and oxidation, ductile, alloys readily, magnetic properties, can be deposited by electroplating and has catalytic properties.

2. How do we measure it?

Measuring nickel (Ni) exposure is both simple and complex. It is simple in the sense that it involves standard inhalable particulate measurements to AS 3640 (2009) followed by chemical analysis for nickel. Chemical analysis is typically by inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma mass spectrometry (ICP-MS), or x-ray fluorescence (XRF) using NIOSH method[1] 7300 or MDHS[2] 91/2, respectively. It should be noted that the inhalable sampler collects around 2-fold higher Ni mass than the 37 mm (total aerosol in closed-face mode) sampler (Tsai *et al*, 1996). Most epidemiology data has been based on total aerosol collection, not inhalable particulate.

Complexity comes where speciation is required. Epidemiologists generally divide nickel species into four broad categories:

- *sulphidic nickel*, where the species nickel sub-sulphide is of particular interest;
- *oxidic nickel*, which includes high and low temperature nickel oxide, nickel hydroxide and carbonate and other sparingly soluble species;
- *soluble nickel*, including nickel sulphate and chloride; and
- *nickel metal*.

When considering nickel exposures present in epidemiologic studies, the estimates of metallic, soluble, sulphidic and oxidic nickel substances made in the 1990s were usually based on the results of the Zatka speciation method applied to aerosol samples (Conard *et al*, 2008). This method separates the species based on their aqueous solubility and mimics, but is not identical with, lung fluid solubility. It is critical for practitioners of sequential leaching techniques to recognize potential limitations and to use professional judgment when interpreting results.

It should be noted that a recent review found that few laboratories were able to analyse Ni at a limit of quantitation (LoQ) that could quantitate 10% of the Scientific Committee on Occupational Exposure Limits (SCOEL, 2011) OEL of 0.01 mg Ni/m^3 (i.e. 1 µg/sample when 8 hours sampled). Those laboratories that could meet that standard generally employed ICP-MS analysis. Consultation with the laboratory is required to ensure an adequately low LoQ is available.

ICP-MS and ICP-AES are the most common analytical methods used to determine "total nickel" concentrations in biological materials such as blood, tissues, urine and faeces. There have been studies to correlate nickel in air with nickel in urine. Formulae have been derived, which are provided in German EKA Documentation for readily soluble nickel (Deutsche Forschungsgemeinschaft (DFG), 2010) and sparingly soluble nickel (DFG, 1995). More recent comparisons have been provided between personal monitoring air samples and nickel in urine for both readily soluble and sparingly soluble nickel by Thomassen *et al* (1999). While there is good agreement between Thomassen *et al* and DFG (noted above) for readily soluble nickel, there is not the same agreement for sparingly soluble nickel. The correlation provided by Thomassen *et al* is more recent and the species of nickel have been directly determined as part of the study. The AIOH therefore believes that the formula provided by Thomassen *et al* (1999) provides a better estimate for correlating airborne sparingly soluble nickel with urinary nickel.

3. Hazards associated with nickel and its compounds

The hazards from exposure to nickel appear to have been first recognized during the period of the 14th to 17th century. Agricola referred to the toxic effects of cupronickel ores on the lungs of workers in the Schneeberg area in Germany (Sunderman, 1989). Inhalation is the main route of exposure to nickel in industry, although ingestion of nickel dust from contaminated skin may also be an exposure route (Lauwerys & Hoet, 2001, p 160).

Nickel metal and its insoluble compounds are poorly absorbed dermally, whilst some nickel compounds such as nickel chloride and nickel sulphate can be absorbed into the skin (Fullerton *et al*, 1986; US Department of Health and Human Services, 2005). NiPERA in general use 2% for dermal absorption from soluble compounds and 0.2% from nickel metal. So overall the dermal route is only a concern for local effects (Oller, 2015, pers comm).

It should be noted that there is disparity in the literature and between organisations on what the main health endpoints (sentinel effects) are. Different organisations have used different critical effects to derive exposure limits.

The Safe Work Australia (SWA, 2015) document "Deemed Diseases in Australia", which reviews the latest scientific evidence on the causal link between diseases and occupational exposures, determined that the diseases caused by nickel compounds were:

- nasal cavity and para-nasal sinus cancer;

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[1] Available from http://www.cdc.gov/niosh/docs/2003-154/

[2] Available from http://www.hse.gov.uk/pubns/mdhs/

- lung cancer; and

- contact dermatitis.

The SWA (2014) HSIS provides the following classifications as to health effects for nickel and its compounds, based primarily on European Commission classifications:

Nickel Compound	Sensitiser	Carcinogen
Nickel, metal & powder	H317, may cause an allergic skin reaction.	Group 2B, suspected carcinogen; H351, limited evidence of carcinogenic effect; H372, causes damage to organs through prolonged or repeated exposure.
Nickel, soluble compounds (as Ni)	H317/334, may cause an allergic skin reaction, allergy or asthma symptoms or breathing difficulties if inhaled; H315-318, causes skin irritation/ causes serious eye damage.	Group 1, established human carcinogen; H350i, may cause cancer by inhalation; Mutagen Cat. 3; H341, suspected of causing genetic defects; Repr Cat 2; H360D, may damage the unborn child; H372, causes damage to organs through prolonged or repeated exposure; H332/302 or H331/301, harmful or toxic by inhalation / if swallowed.
Nickel sulphide roasting (fume & dust) (as Ni)	H317, may cause an allergic skin reaction.	Group 1, established human carcinogen; H350i, may cause cancer by inhalation.

Respiratory cancer

Epidemiological studies of workers employed in the production of nickel have shown an association between exposure to nickel compounds and lung and nasal cancer. In 2012, IARC classified nickel compounds as being carcinogenic to humans (Group 1). The compounds principally implicated are sulphidic nickel, particularly nickel sub-sulphide (Ni_3S_2) and oxidic nickel, which includes a range of insoluble nickel compounds.

There is debate about whether soluble nickel compounds are carcinogenic. Oller (2002) concluded that the weight of evidence indicates that inhalation exposure to soluble nickel alone will not cause cancer. However, Oller conceded that if soluble nickel is inhaled at concentrations high enough to induce chronic lung inflammation, these compounds may enhance carcinogenic risks associated with inhalation exposure to other substances. Further, evidence clearly indicates that these compounds strongly increase the potency of oxidic nickel compounds and should be considered carcinogenic (Goodman *et al*, 2009).

Metallic nickel is considered a Group 2B suspected carcinogen by IARC (2012), but is also classified as not suspected as being carcinogenic (e.g. ACGIH, 2015; SCOEL, 2011).

Respiratory non-cancer effects (e.g. inflammation, fibrosis, pneumoconiosis, COPD)

Inhalation studies in rats and mice exposed to several nickel compounds and nickel metal powder have all indicated that at certain exposure levels, adverse respiratory effects on the lung and nose can be observed (e.g. chronic lung inflammation, fibrosis, changes in nasal epithelium) (Oller *et al*, 2014). While most epidemiological studies have not shown an association between nickel exposures and increased mortality due to non-malignant respiratory disease, one study of x-ray abnormalities indicated a statistically significant association between mild x-ray abnormalities and cumulative exposures to water soluble and sulphidic nickel compounds. Humans do not appear to be as sensitive as rats to fibrotic lung responses (Oller *et al*, 2014).

Sensitisation

Skin and respiratory sensitisation are potential health effects as a result of exposure and some individuals are more prone to being sensitised. It is also important to know that once a person is nickel-sensitised then this is not reversible. Cases of respiratory sensitisation are rare. There are a few reports of asthma cases associated with inhalation exposure to water soluble nickel compounds in the plating industry. The significance of these few cases is unclear, given the tens of thousands of workers that have been exposed to soluble nickel compounds in the last 50-60 years.

According to Oller *et al* (2014, p 570), although nickel sulphate is considered a respiratory sensitiser "there are no animal or human data suitable to conduct a risk assessment for this health endpoint".

Recent information has also indicated that exposure to relatively low concentrations of nickel via the oral route (ingestion) can exacerbate adverse health effects in nickel-sensitised individuals (European Food Safety Authority, 2015). Antico and Soana (2015, p e56), have also concluded that nickel sensitisation and dietary nickel seem to be the chief trigger for provocation and persistence of symptoms of patients with chronic allergic-like dermatitis syndromes.

The development of allergic reactions to nickel has been correlated with specific CD8 plus T cells that induce cell death to nickel-laded keratinocytes, which is the predominant cell type in the outermost layer of the skin. In non-allergic individuals, the circulating CD8 plus T cells reactive to nickel are lacking. CD8 plus T cells can therefore be measured to identify individuals that are hypersensitive (Cavani *et al*, 1998).

Reproductive effects

An adverse reproductive effect (increased perinatal mortality) has been seen in female animals ingesting large doses of a water soluble nickel compound in single and multi-generation reproductive studies. A reproductive study of female Russian refinery workers has not unequivocally

demonstrated an association between relatively high soluble nickel exposures and reproductive outcomes including genital malformations, spontaneous abortions, small-for-gestational-age newborns and skeletal malformations (Vaktskjold *et al*, 2006; 2008a; & 2008b). This position paper considers the Vaktskjold *et al* studies to be inconclusive due to study defects.

Never the less, the European Union has classified some forms of nickel as reproductive category 2 (based on animal studies), H360D, which is attributed to chemicals that may damage the unborn child.

4. Major uses / potential for exposure (in Australia)

Nickel exposure in Australia is predominately in the mining and smelting operations, although exposure in welding may be significant.

Nickel mining resources are divided principally between nickel sulphide and laterite (oxide) deposits. Historically, production has been dominated by sulphide ores but future production is increasingly shifting to laterite ores. Sulphide ores have dominated because they are easier to process through conventional mining, smelting and refining, compared to laterite ores. Laterite ores require intensive hydrometallurgical processing such as high pressure acid leaching (HPAL). This means that laterite ores typically require substantially more energy and chemicals to produce than sulphide nickel. Primary nickel is produced and used in the form of ferro-nickel, nickel oxides and other chemicals, and pure nickel metal. Nickel is also readily recycled from many of its applications, and large tonnages of secondary or "scrap" nickel are used to supplement newly mined metal. Worldwide, about 1.4 million tonnes of new or primary nickel are produced and used annually.

Australia has about 30% of the world's nickel reserves and a high proportion of this is high-grade. Australia's nickel production in 2014 amounted to 220 kilotonnes (kt), most from Western Australia (>95%). Most of the nickel ore mined in Australia is processed locally into nickel concentrate by downstream smelting and refining firms. The value of all nickel products exported in 2012 was $4.005 billion and was Australia's eighth most valuable mineral and petroleum export commodity. Australia in 2014 was the world's fifth-largest nickel producer behind the Philippines (440 kt; 18.3%), Russia (260 kt; 10.8%), Indonesia (240 kt; 10.0%) and Canada (233 kt; 9.7%), accounting for 9.2% of estimated world mine production.

About 85% of nickel is used in alloying to produce stainless, heat-resisting and other steels, often for highly specialized industrial, aerospace and military applications due to their corrosion resistance in aqueous, gaseous and high temperature environments, their mechanical properties at all temperatures from cryogenic to the very high, and occasionally for their special physical properties. About 9% is used in plating where it imparts hardness and wear and corrosion resistance. The remaining 6% finds other uses, including coins, electronics, in nickel metal hydride rechargeable battery systems, and as a key ingredient in many catalysts.

Further information is also available from the Nickel Institute.[3]

5. Risk of health effects

The most significant review of nickel epidemiology was conducted by the International Committee on Nickel Carcinogenesis in Man (ICNCM). This committee was established in 1984 under the Chairmanship of British epidemiologist Sir Richard Doll and its report was published in 1990 (Doll, 1990). The committee considered the exposures and cancer health outcomes of 14 cohorts which covered most nickel workers internationally. ICNCM found that "*although much of the respiratory cancer risk seen among the nickel refinery workers could be attributed to exposure to a mixture of oxidic and sulphidic nickel at very high concentrations, exposure to large concentrations of oxidic nickel in the absence of sulphidic nickel was also associated with increased lung and nasal cancer risks. There was also evidence that soluble nickel exposure increased the risk of these cancers and that it may enhance risks associated with exposure to less soluble forms of nickel.*"

Since that time, a study by Egedahl *et al* (2001) found no evidence implicating nickel concentrate or metallic nickel in the hydro-metallurgical refining process with increased lung cancer. In contrast, a study by Arena *et al* (1998) of 31,165 workers from 13 high nickel alloy plants throughout the US showed that overall, white male nickel workers have a 13% greater relative risk of lung cancer in comparison to the US population and little or no excess relative to the local population.

Animal studies

The US National Toxicology Program (NTP) conducted two year toxicology and carcinogenesis studies. The final reports for these studies were issued in 1996 and were also cited in Dunnick *et al* (1995). The studies were for: nickel sulphate hexahydrate (NTP, 1996a), nickel sub-sulphide (NTP, 1996b) and nickel oxide (NTP, 1996c).

Compound	Animal	Exposure Concentrations
NiO	Rat	0, 0.62, 1.25, or 2.5 mg nickel oxide/m^3
	Mouse	0, 1.25, 2.5, or 5 mg nickel oxide/m^3
Ni_2S_3	Rat	0, 0.15, or 1 mg nickel sub-sulphide/m^3
	Mouse	0, 0.6, or 1.2 mg nickel sub-sulphide/m^3
$Ni_2SO_4.6H_2O$	Rat	0, 0.12, 0.25, or 0.5 mg nickel sulphate hexahydrate/m^3
	Mouse	0, 0.25, 0.5, or 1 mg nickel sulphate hexahydrate/m^3

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[3] Nickel institute http://nickelinstitute.org

The results of these studies in relation to carcinogenic potential are summarised in the following table:

Animal	NiO	Ni$_2$S$_3$	Ni$_2$SO$_4$.6H$_2$O
Male Rats	Some evidence	Clear evidence	No evidence
Female Rats	Some evidence	Clear evidence	No evidence
Male Mice	No evidence	No evidence	No evidence
Female Mice	Equivocal evidence	No evidence	No evidence

In both studies non-carcinogenic effects were identified in all animals at each concentration.

The case for lung fibrosis from exposure to metallic nickel is based on a study initially established to determine the carcinogenicity of rats to nickel metal powder (Oller *et al*, 2008). While the study was negative for carcinogenicity, and in that sense confirming the results of human studies (Doll, 1990; Sivulka & Seilkop, 2009), it was found that 1.0 mg/m^3 was not tolerated by the rats and a maximum tolerated dose of 0.4 mg/m^3 was established, although animals exposed to 0.1 mg/m^3 showed adverse lung effects, meaning a LOAEL and not a NOAEL was determined. From this starting point SCOEL derived 0.005 mg/m^3 as an OEL for respirable nickel.

The most sensitive animal test species (the rat) has shown evidence of carcinogenicity at 0.15 mg/m^3 as nickel sub-sulphide (corresponding to 0.11 as Ni mg/m^3) (Dunnick *et al*, 1995), which was the lowest exposure that induced tumours in the NTP 1996c study (cited in Goodman *et al*, 2009, p 401). The available animal data on developmental toxicity provides suggestive evidence that the developing foetus and neonates are sensitive targets of nickel toxicity (US Department of Health and Human Services, Agency for Toxic Substances Disease Registry (ASTDR) 2005 p 120).

Human studies – cancer studies

Repeated studies have found that cancer incidence of the Clydach cohort has been indistinguishable from background following a plant upgrade which reduced exposures in 1950. The most recent follow-up of those workers (Sorahan, 2004; Sorahan & Williams, 2005) reported an overall non-significant excess of lung cancer in workers employed after 1952. However, a significant excess was noted for one specific sub-group where exposure was in the range 1 to 10 mg/m^3 until 1975 when it was reduced to 1 to 2 mg/m^3. In the pre-1950 period lung and nasal cancers were common and were generally attributed to exposure to nickel sub-sulphide and oxidic nickel.

Sivulka *et al* (2014) reassessed exposures at Clydach over the period 1950 to 2005; measurements after 1975 were based on personal exposure. Caution is required in interpreting this data as exposure is presented as geometric means (GMs) and two thirds of the accompanying geometric standard deviations (GSDs) exceeded a value of 3 and many exceeded 4 or 5. Exposure levels in the range 0.1 mg/m^3 to 0.5 mg/m^3 were reported, with those in the lower end of the range more common. Based on these GSDs the GM presented could reasonably be doubled to provide true average exposures between 0.2 mg/m^3 and 1 mg/m^3. This study has reduced the estimates of exposure established by Doll by about 50%.

On the other hand, a reassessment of exposures at Kristiansand by Grimsrud *et al* (2002), based on an earlier reconstruction of exposures, showed that soluble nickel is responsible for ongoing lung cancer cases. This is at odds with most other exposure assessments. The main species implicated in the carcinogenicity was soluble nickel while in other studies and in the animal data presented above nickel sub-sulphide and to a lesser degree oxidic nickel are implicated with soluble Ni of much lower carcinogenic potential. Oxidic nickel in the presence of soluble nickel has been found carcinogenic by others including Doll.

Further uncertainty exists with the dose response curves presented in the Grimsrud *et al* (2002) reassessment. Only in the case of water soluble nickel does the curve increase monotonically. In the case of both sulphidic and oxidic nickel the risk increases rapidly with any exposure (maxima occur at about 0.06 and 0.10 mg/m^3 x years respectively) and then decreases as cumulative exposure increases; a biologically implausible super linear exposure response function (Goodman *et al*, 2009). Metallic nickel shows an increased risk but not significantly so. In the assessment of all plants the risk of cancer reduced over the years as plant improvements reduced exposures; again at odds with Grimsrud *et al*'s findings.

Grimsrud *et al*'s 2002 risk assessment also uses median exposure rather than arithmetic mean (AM) even though the latter was included in the earlier paper (Grimsrud *et al*, 2000). Using AM would increase the exposure estimate by 50 to 100%; GSDs were variable up to 3.2. Additionally, exposure was measured as total dust rather than the current inhalable particulate fraction. A factor of two may be appropriate to convert the data to estimate the inhalable dust fraction, resulting in a further doubling of the exposure estimate.

While caution with the data is required, there was a significant increase in lung cancer incidence (odds ratio) for water soluble nickel observed at a cumulative exposure of 1.6 mg/m^3 x years, equivalent to 0.04 mg Ni/m^3 when calculated for 40 years of exposure (95% confidence intervals 1.0, 6.0) (Grimsrud *et al*, 2002). Adjusting the exposure as suggested above, 0.04 mg/m^3 becomes 0.1 mg/m^3 as the inhalable fraction.

The 1998 study by Anttila *et al* at the Harjavalta plant in Norway supports the Grimsrud *et al* position. However, in the Port Colbourne cohort in Canada (Heller *et al,* 2009), electrolysis workers who were exposed exclusively to soluble nickel showed no excess respiratory cancer as did the NTP animal studies, which found soluble nickel was not carcinogenic. It is suggested that the reason for the increase in respiratory cancer in Kristiansand electrolysis workers is due to their exposure to "mixed nickel species", not only soluble nickel. Heller *et al* (2009) when contrasting the difference between the incidences of cancer attributed to soluble nickel at Port Colbourne (no excess) and Kristiansand (main species implicated) noted that the layout of the plants was vastly different. Port Colbourne is spread over a large area so that each department was independent of the others while Kristiansand was a multistorey plant where emissions from one department would necessarily influence exposure and the nickel species of the exposure in the other departments. The extent of this cross exposure, if any, is debated.

There are difficulties and uncertainties in using epidemiological data to estimate levels (and types) of nickel exposure that correspond to increased respiratory cancer risk in nickel refinery workers. They can include absence of exposure measurements, inability to estimate and account for mixtures of different forms of nickel, and the presence of and possible interactions with other potential confounding hazards such as cigarette smoking. Never the less, human studies are preferred for informing derivation of an appropriate OEL. For the most part, different studies of workers occupationally exposed to nickel are reasonably consistent in suggesting that increased lung cancer risk occurs at inhalable nickel concentrations that are above 0.1 mg/m^3 (Oller *et al*, 2014; Goodman *et al*, 2011).

Human studies – non cancer studies

Lung fibrosis drives the SCOEL OEL for metallic nickel of 0.005 mg/m³ in respirable dust based on the animal study of Oller *et al* (2008).

Review of the literature of human exposure to metallic nickel, and in fact all nickel species, presents a different picture. Berge and Skyberg (2003) in a study of pulmonary fibrosis at Kristiansand found a prevalence of 4.5% of workers with pulmonary fibrosis at greater than ILO category 1/0, although only 6 of the 1046 workers reviewed exceeded ILO category 1/1. Pulmonary fibrosis was significantly associated with exposure to soluble and sulphidic nickel but not to metallic nickel. It should be noted that 74 workers were identified as having pleural plaques suggesting asbestos exposure. Twenty one of the 47 workers diagnosed with pulmonary fibrosis also had pleural plaques. The authors stated the estimated asbestos exposure was not correlated with pulmonary fibrosis. Cox *et al* (1981) investigated respiratory mortality in a plant where exposure to metallic nickel was around 2.5 mg/m³ reducing over time to between 0.4 and 0.9 mg/m³. They found that there were reduced standardised mortality ratios (SMRs) for both respiratory cancer and other respiratory disease. While this is a mortality study, both the level and period of exposure are such that increased SMR were likely if metallic nickel posed a significant fibrogenic risk.

Egedahl *et al* (2001) reviewed workers' respiratory mortality in a hydrometallurgical nickel refinery plant where exposure to metallic nickel had averaged 4 mg/m³. While no cancer effects were associated with metallic nickel exposure they also found no excess of mortality due to non-cancer respiratory disease. SMRs were reduced but not significantly so.

Sorahan & Williams (2005) in a study of workers at Clydach found that mortality due to non-malignant causes of the respiratory tract showed no overall excess. Arena *et al* (1998) in a study of high alloy nickel workers found no evidence for increased mortality due to non-malignant respiratory mortality. Muir (1993) studied workers at the INCO Copper Cliff sinter plant at Sudbury who had shown a significantly increased risk of lung and nasal cancer, the result of high nickel exposure. He concluded "*The prevalence of irregular opacities in the sinter plant workers was similar to that in published studies of smoking populations and those exposed to dusts of low fibrogenic potential. This is evidence against the hypothesis that dusts containing nickel can cause a significant fibrotic response in human subjects and is in accord with mortality studies that have not shown evidence of an increase in the risk of death as a result of non-malignant respiratory disease.*"

That there is a paucity of other human data on pneumoconiosis when malignant disease of the respiratory system was common and being investigated through health surveillance suggests that nothing was suspected for fibrotic effects. In these circumstances an OEL based on the effects observed in a study on rats and which is not supported by human data seems overly conservative and unnecessary.

6. Available controls

Detail on the control of nickel exposures can be found on the NiPERA website.[4] The control of nickel in most applications aligns with those controls used in the management of general particulate. In electrowinning it may be necessary to limit the generation of nickel containing mists. Control implementation should follow the hierarchy of controls.

- Efficient ventilation – Areas with activities likely to generate harmful particulate or fume concentrations should be enclosed if practicable, and well ventilated (exhaust ventilation). The generation of mists during electrowinning may be reduced by covering the cells or addition of surfactant to modify the surface tension and reduce generation of mist.

- An alternative to source containment and ventilation is worker enclosure; e.g. provide cabs on vehicles or enclosed control rooms with filtered / pressurised / air-conditioned air supply. Where ventilation systems are installed, these systems should be maintained in good working order and should be operated in the correct manner to provide optimum protection from dust /fume exposure.

- Inspection and maintenance routines for engineering controls and worker enclosures, and periodic formal review of the practicality of engineering controls, are essential administrative controls. The periodicity of these activities will vary according to the health risk associated with the hazard being controlled and the functionality of the control being used.

- Good housekeeping - The maintenance of a high standard of housekeeping will minimise exposure to particulate. Methods of wet cleaning can be used in some circumstances where downstream contamination is not an issue.

- The provision of regular education and training is particularly important as employees need to understand the different routes of exposure and the impact on how they approach their work. The conduct of workplace and employee in-air monitoring and health surveillance of employees may also be considered a part of the controls for mitigating exposures.

- Administrative controls - A reduction of level and duration of exposure of employees may be achieved by work organisation and limits on overtime. The principle of periodic rotation of employees both through and in areas with potentially harmful dust and fume exposures is an acceptable practice; this should however be restricted to only plant-trained employees.

- Where practicable a clean/dirty change-room process similar to that employed in the lead industry should be utilised. Work clothing should not be taken home where there exists a risk of cross contamination with domestic laundry.

- Good hygiene must be practiced in areas where potential exposure may occur and no eating, drinking and smoking allowed in these areas.

- Provision and sensible use of personal protective equipment (PPE) – Half-face respirators when worn correctly, will normally provide adequate protection against dust exposures. In all cases the respiratory protection program should follow the requirements of AS/NZS 1715, "Selection, Use and Maintenance of Respiratory Protection Devices". PPE should be used as a last resort, where other control measures have been unsuccessful.

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[4] NiPERA (Nickel Producers Environmental Research Association) Workplace Guide – see http://www.nickelinstitute.org/NiPERA/WorkplaceGuide.aspx

It is important to emphasize that there is a need to establish, embed and continue to maintain control systems and to put in place methodology for ongoing auditing and measurement of their effectiveness.

PPE used alone is the least effective option for controlling exposure. It should always be used in combination with other methods of exposure control.

Recent research undertaken by the UK HSE (2013) has demonstrated the value of using urinary nickel as a measure of control effectiveness for workplaces where skin contamination, hence inadvertent hand mouth contact and ingestion, may be an issue (i.e. electroplating). This has provided the impetus to further reduce urinary nickel levels by up to 40% in electroplating shops in the UK. Caution must however prevail when developing a biological monitoring program as increased nickel in body fluids can result from sources other than occupational exposure (i.e. dialysis, diet) (Nieboer & Nriagu, 1992).

7. Current applicable legislation and standards

Occupational exposure limits (OELs) for nickel across international jurisdictions vary by at least one order of magnitude, which adds to the complexity of a harmonized approach to setting occupational exposure limits. The current SWA workplace exposure standards (WES) for nickel and its compounds were derived from the ACGIH 1991 version of the *Documentation of Threshold Limit Values and Biological Exposure Indices* (6th Edition). Expressed as time weighted average 8 hour (TWA-8hr) values, they are:

- Nickel metal 1.0 mg/m^3 (Sen)
- Nickel sulphide roasting (fume & dust) (as Ni) 1.0 mg/m^3 (Sen)
- Nickel, soluble compounds (as Ni) 0.1 mg/m^3 (Sen)

In June 2011, the SCOEL recommended OELs for nickel and inorganic nickel for consideration by the European Member States to adopt into their legislation, as follows (expressed as TWA-8hr values):

- Inhalable nickel 0.01 mg/m^3 (excluding nickel metal)
- Respirable nickel 0.005 mg/m^3

The 1996 ACGIH (still current in 2015) TWA-8hr TLV® values for nickel and inorganic compounds including nickel sub-sulphide (as inhalable Ni) are:

- Elemental 1.5 mg/m^3 (A5 – dermatitis; pneumoconiosis)
- Soluble inorganic compounds (NOS) 0.1 mg/m^3 (A4 – lung damage; nasal cancer)
- Insoluble inorganic compounds (NOS) 0.2 mg/m^3 (A1 – lung cancer)
- Nickel sub-sulphide 0.1 mg/m^3 (A1 – lung cancer)

Nickel and its inorganic compounds were on the ACGIH notice of intended changes (NIC) but have since been withdrawn – it is not on the 2015 NIC. The 2001 NIC was for a TLV of 0.05 mg/m^3 for all nickel compounds as total aerosol.

NIOSH has a recommended exposure limit (REL) of 0.015 mg/m^3 for elemental nickel and all nickel compounds, excluding nickel carbonyl.

There are currently no biological exposure indices (BEI) for nickel, although it is on the ACGIH 'Under Study' list. SCOEL (2011) have recommended a biological guidance value (BGV) of 3 µg/L in urine based on background levels in a working age population. As such, it is not health based or an indication of risk and can only be considered as a guideline value when assessing effectiveness of exposure controls such as personal protective equipment (PPE).

There should be caution when applying the SCOEL biological guidance value as this has not considered a range of populations. A more realistic urinary nickel reference value has been proposed by Hoet *et al* (2013), which covers a range of countries and populations. They recommend an upper reference limit (URL) equivalent to a 97.5[th] percentile of nickel in urine for a general adult population of 6 µg/L. Tomassen *et al* (1999) determined an airborne equivalent correlation between external exposure levels of sparingly soluble nickel compounds and urinary levels of nickel, whereby 0.1 mg/m^3 exposure was equivalent to 10 µg /L in urine.

Even then caution should be exercised as ingestion may bias results and provide a false indication that respiratory protection is ineffective.

Urinary nickel concentration can be considered an index of foetal exposure since it is proportional to serum nickel (Thomassen *et al*, 1999; Vaktskjold *et al*, 2006).

This position paper strongly recommends against deriving health-based biological exposure limits from the tolerable daily intake (TDI) using drinking water quality guidelines. This is because nickel exposure will also be via inhalation, which will be absorbed into the body at different rates, depending on solubility and extent that species are mixed, as well as affecting target organs differently (i.e. lung).

8. AIOH RECOMMENDATION

The animal data for fibrotic effects of sulphidic, oxidic and soluble nickel (NTP, 1994a; 1994b; & 1995) and for metallic nickel (Oller *et al*, 2008) are unconvincing when viewed in the light of human epidemiology. Reproductive outcomes, either animal or human, do not occur at the exposure levels of interest. For nickel compounds in general, the main adverse health effects that need to be considered in setting an OEL are respiratory cancer (of the lung and nasal cavity and para-nasal sinus) and sensitisation leading to contact dermatitis. The AIOH regards respiratory cancer (lung and nasal) as the main health effect to derive an OEL recommendation.

The compounds principally implicated in causing respiratory cancer are sulphidic nickel, particularly nickel sub-sulphide (Ni_3S_2) and oxidic nickel, which includes a range of insoluble nickel compounds. There is debate about whether soluble nickel compounds are carcinogenic, although respiratory cancer risk is greater when there is exposure to mixed species of nickel.

The exposure review at Clydach (Sivulka *et al*, 2014) found exposures in the range 0.2 to 0.5 mg/m³ over the past 40 years based on personal sampling. The review of respiratory cancer incidence (Sorahan, 2004; Sorahan & Williams, 2005) found a small non-significant overall increased risk of respiratory cancer in a sub-cohort exposed to over 1 mg/³ The available epidemiological data provide little, if any, evidence of elevated lung cancer risks at inhalable exposures to total aggregated forms of nickel less than 0.2mg/m³ (Goodman *et al* (2011) cited in Oller *et al*, 2014).

Using this data, a cautious approach would lead to an OEL of around 0.1 mg/m³. The occurrence of multiple species in most work environments and the difficulty in speciation suggest a common limit for all species.

Accordingly, the AIOH recommends an exposure standard for all forms of nickel of 0.1mg Ni/m³, to be measured as the inhalable aerosol fraction according to AS 3640.

Regarding the potential for reproductive toxicity and sensitisation, this position paper recommends the precautionary principle approach. This means that extra care should be taken to avoid skin contact which will reduce inadvertent hand-mouth contact and subsequent exposure from ingestion. Biological monitoring is recommended for nickel as a complementary measure of exposure (not health effect).

A precautionary guideline value of 10 µg/L nickel in urine is recommended as being more or less equivalent to sparingly soluble airborne nickel (Tomassen *et al*, 1999); above this may indicate work practices that are not best practice. Establishing a baseline using urinary nickel level can be used as a measure of control effectiveness for workplaces where inhalation, or skin contamination, hence inadvertent hand mouth contact and ingestion, may be an issue (i.e. electroplating) and drive continuous improvement.

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